CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CACODYLIC ACID

Chemical Code # 32, Tolerance # 311
SB 950 # 27

October 23, 1992
Revised: 6/7/93, 10/17/94, 5/10/95, 2/20/96

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 144422 and 913606 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T960220
Prepared by Stanton Morris, 2/20/96

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****311-039 092715**, "Cacodylic Acid, Combined Chronic Feeding and Oncogenicity Study in the Rat"; E. Gur, A. Nyska, T. Waner, and S. Crown; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/010/CAC; 10/30/89. Cacodylic acid (99.34% stated purity, batch # 1007) was fed in the diet of 60 Fischer F344 rats/sex/group for 2 years at 0, 2, 10, 40, or 100 ppm. Treatment-related effects were: increased water intake in both sexes at 40, and 100 ppm; increased kidney weights in both sexes at 100 ppm; decreased adrenal weights in females at all doses; morphological changes of thyroid follicles and increased histopathology pathology findings of the kidney in males at 10 ppm and both sexes at 40 and 100 (non-oncogenic NOEL = 10 ppm). **A possible adverse** effect was indicated by increased urinary bladder transitional cell hyperplasia in males and females at 40 and 100 ppm and papillomas and carcinomas in males at 2, 10, 40, and 100 ppm and females at 100 ppm. The study was unacceptable (H. Green and S. Morris, 5/5/92) but upgraded to acceptable by submission of LSRI Schedule No. PAL/009/CAC and an adequate rationale for the doses used (S. Morris, 4/23/93).

> 311-048 121943; "Cacodylic Acid Toxicity in Dietary Administration to Rats for 13 Weeks: A Preliminary Study"; S. Crown, G. Kenan, A. Nyska, and T. Waner; LSRI Report No. PAL/009/CAC; Life Science Research Israel Ltd., Ness Ziona, Israel; 5/87. Ten Charles River CDF (Fisher 344) rats/sex/group were exposed for 13 weeks to dietary mixtures of the test material at 0, 5, 50, 500, 2000, or 5000 ppm. All animals in the 5000 ppm group died or were sacrificed in extermis within the first two weeks of treatment and all of those in the 2000 ppm group died or were sacrificed in extermis within the first four weeks of treatment. Two rats/sex also died at 500 ppm. The mortalities were associated with abnormal clinical signs and macro and/or microscopic pathologies of the gastrointestinal track, kidneys, heart, bone marrow, spleen, thymus, testes, aorta, and thyroid. In the rats surviving to term, terminal body weights for the 500 ppm males and females were respectively 92 and 94% of controls. There were a variety of mild to moderate, treatment-related effects in males and/or females at 50 and/or 500 ppm that included: abnormal clinical signs, increased water consumption, decreased erythrocyte values, changes in blood and urine chemistry, macroscopic changes of the stomach and adrenals, and microscopic changes in the stomach, kidneys, thyroids, heart, spleen, testes, uterus, aorta, bone marrow, and thymus. Evaluation of these data resulted in acceptability status for the chronic feeding and oncogenicity test types being changed from "unacceptable, inadequate study" to "no data gap (see DPR Worksheet, S. Morris, 4/23/93)

Note: The possible adverse effect is listed under the oncogenicity test type because of the nature of the effect (S. Morris, 4/23/92).

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

CHRONIC TOXICITY, DOG

** 311-033 085701, "Cacodylic Acid 52-Week Oral Toxicity Study in Beagle Dogs"; G. Zomber, A. Nyska, T. Waner, M. Pirak, and S. Crown; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/012/CAC; 11/21/89. Groups of 5 Beagle dogs / sex were given cacodylic acid

(99.8% stated purity, batch # 1007) orally in gelatin capsules at 0, 6.5, 16, or 40 mg/kg/day, 6 days/week for 52 weeks. Treatment-related effects were: increased salivation, vomiting, and diarrhoea in both sexes at 6.5, 16, and 40 mg/kg/day (NOEL < 6.5 mg/kg/day); transient changes in hematology parameters and serum enzymes and increased liver size in males at 40 mg/kg/day; and decreased body weight gains with group mean body weights always being > 85% of controls and decreased plasma albumin and calcium in both sexes at 40 mg/kg/day. No adverse effect was indicated. The study was unacceptable because overt toxicity was not demonstrated at the high dose (J. Kishiyama and S. Morris, 4/23/92) but upgraded by submission of an adequate rationale for the doses used (S. Morris and J. Gee, 10/17/94).

311-050 122383, "Cacodylic Acid 90-day Toxicity Study in Beagle Dogs: A Preliminary Study", A. Reiss, A. Nyska, and T Waner; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/011/CAC; May, 1987. Four beagle dogs/sex were dosed orally with the test material in capsules for 90 days at 0.0, 5.0, 15.5, or 48 mg/kg/day. At the end of the third week, the 5.0 mg/kg/day group was raised to 72 mg/kg/day and a group of 2 dogs/sex were added at 108 mg/kg/day. Two of the four and both of the females in the respective 72 and 108 mg/kg/day groups were killed in extremis. Treatment-related effects included: increased vomiting, diarrhea, and salivation seen at 48, 72, and 108 mg/kg/day; decreased body weight gain and food consumption in males at 72 and 108 mg/kg/day and females at 48, 72, and 108 mg/kg/day; haematological changes in males at 108 mg/kg/day; and reduced organ weights in both sexes. Evaluation of these data resulted in no change in status for the study at DPR doc. # 311-033, rec. # 085701 (see DPR Response 6/7/93). No worksheet was done (S. Morris, 6/7/93).

311-050 122384: This document contains comments about DPR's findings in the study at DPR doc. # 311-033, rec. # 085701 but no new data. Evaluation of these comments resulted in no change in study status (see DPR Response 6/7/93). No worksheet was done (S. Morris, 6/7/93).

ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

311-040 097564; "Cacodylic Acid Oncogenicity Study in the Mouse", LSRI Project No. PAL/014/CAC; E. Gur, A. Nyska, M. Pirak, T. Waner and S. Crown; Life Science Research Israel Ltd., Ness Ziona, Israel; 12/12/89. Cacodylic acid (99.5%, batch # 1007) was fed in the diet to 55 B6C3F1 mice/sex/dose at 0, 8, 40, 200, or 500 ppm for 2 years. Treatment-related effects were a decrease mean male body weight gain at 500 ppm and transiently at 200 ppm with all group mean body weights being > 90% of controls and increases in water intake and pancreatitis in males at 500 ppm. A **possible adverse effect** was indicated by treatment-related increases in: nephrocalcinosis in males at 500 ppm; glomerulonephropathy in males at 200 and 500 ppm and females at 500 ppm; vacuolar degeneration of the urinary bladder transitional epithelium in males at 200 and 500 ppm and females at 40, 200, and 500 ppm (non-oncogenic NOEL = 8 ppm); and multiple-organ fibrosarcomas in males at 40, 200, and 500 ppm and females at 500 ppm. The study is unacceptable but possibly upgradeable with submission of an adequate rationale for the highest dose (S. Morris and J. Gee, 6/26/92).

311-047 121942; "Cacodylic Acid Toxicity in Dietary Administration to Mice for 13 Weeks: A Preliminary Study"; LSRI Report No. PAL/013/CAC; S. Crown and A. Nyska; Life Science Research Israel Ltd., Ness Ziona, Israel; 5/87. Twelve B6C3F1 mice/sex/group were exposed for 13 weeks to dietary mixtures of the test material at 0, 5, 50, 500, 2000, or 5000

ppm. All animals at 5000 ppm died or were sacrificed in extermis within the first 8 weeks of treatment. Terminal body weights for the 500 ppm males and females were respectively 85 and 95% of controls. Water intake was elevated in the 500 and 2000 ppm females. Squamous metaplasia was seen in the colon, cecum, and rectum of both sexes at 2000 ppm. Vacular degeneration of the superficial transitional epithelium of the urinary bladder was seen in both sexes at 500 and 2000 ppm. Evaluation of these data did not result in a change in the study status (see DPR Response 6/7/93). No worksheet was done (S. Morris, 6/7/93).

311-052 144422; "Supplemental Report to Cacodylic Acid Oncogenicity Study in the Mouse", LSRI Project No. PAL/014/CAC, 12/9/95, SM Cohen, Omaha, NE. This document contained an independent evaluation of the study at DPR doc. # 311-047, rec. # 121942. This report may be used in DPR risk assessment evaluations. No worksheet was done (S. Morris 2/2/96).

311-005 913604: "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", J.R.M. Innes et al. (1969), Journal of the National Cancer Institute, 42(6):1101-1114. This document contains summary data on 120 compounds tested in two strains of mice. Eighteen, 7-day-old mice / sex / strain were given cacodylic acid suspended in water by oral gavage at 46.4 mg/kg/day for 3 weeks then in the diet at 124 ppm until approximately 18 months of age. Limited necropsy and histopathology data were collected. Oncogenic effects were not reported for the test material. No adverse effect was indicated. The study is unacceptable and not upgradeable (J. Christopher, 3/4/85).

REPRODUCTION, RAT

311-027 073231, "Cacodylic Acid Two Generation Reproduction Study in the Rat"; Y. Rubin, N. Gal, A. Nyska, M. Pirak, and T. Waner; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/015/CAC; February 5, 1989. A reproduction study was conducted in which cacodylic acid (batch # 1007, 98.7% stated purity) was continuously administered in the feed of Charles River CD rats at concentrations of 0, 3, 21, or 147 ppm for two generations (F0, F1). Twenty-five adult F0 rats/sex/group were exposed for 10 weeks prior to mating then paired. F0 female and F1 conceptus exposures continued through gestation, lactation, and weaning. F0 males were sacrificed after birth of the F1 litters. The protocol was repeated for 25 weanling F1 rats/sex/group until weaning of the F2 pups. Water consumption was elevated in high-dose males and there appeared to be treatment-related, but not toxicologically significant effects on erythrocyte parameters (F0 both sexes, F1 females), oestrus cycling, histological indicators of thyroid activity, and decreased group mean ovarian weight (F1 females) (NOEL = 21 ppm). No adverse effect was indicated. The study was unacceptable because adequacy of dose was not demonstrated by frank toxicity at the high dose. The study was possibly upgradeable by submission of an adequate rationale for the doses used (J. Kishiyama and S. Morris, 4/16/92).

311-049 122337, Exact duplicate of DPR doc. # 311-048, rec. # 121943 (see worksheet and complete one-liner under Combined, Rat). Ten CDF (Fisher F344) rats/sex/dose were exposed for 13 weeks to dietary mixtures of the test material at 0, 5, 50, 500, 2000, or 5000 ppm. All rats in the 2000 and 5000 ppm groups died or were sacrificed in extremis. Two rats/sex died in the 500 ppm group. The mean body weights of the 500 ppm males and females were always $\geq$ 80% and 91% of their respective controls. Other treatment-related effects were similar to those seen in the two-year reproduction study. Evaluation of these data did not result in a change in status for the study at DPR doc. # 311-027, rec. # 073231 (see DPR Response, S. Morris, 6/7/93).

TERATOLOGY, RAT

**** 311-024 069364**, "Cacodylic Acid Teratogenicity Study in the Rat"; N. Gal and Y. Rubin; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/017/CAC; 4/18/88. Groups of 22 pregnant Sprague-Dawley CD rats were administered Cacodylic acid (batch # 1029, 99.8% stated purity, water vehicle) by oral gavage at 0, 4, 12, or 36 mg/kg/day on post coitum days 6 through 15. Maternal effects were reduced food intake and body weight gain at 36 mg/kg/day with group mean body weights always > 95% of controls. A **possible adverse effect** was indicated by fetal effects seen at 36 mg/kg/day: decreased pup weight and length, retarded skeletal development, and increased incidence of diaphragmatic hernia (maternal NOEL = fetal NOEL = 12 mg/kg/day). The study was acceptable (S. Morris and J. Kishiyama, 4/7/92).

TERATOLOGY, RABBIT

** 311-025 069365, "Cacodylic Acid Teratogenicity Study in the Rabbit"; Y. Rubin and A. Nyska; Life Science Research Israel Ltd., Ness Ziona, Israel; LSRI Project No. PAL/019/CAC, 5/5/88. Groups of 15 mated female HY/CR New Zealand White rabbits were given cacodylic acid (batch # 1007, 99.8% stated purity, water vehicle) by oral gavage at 0, 3, 12, or 48 mg/kg/day on gestation days 7 through 19. Does in the high dose group ate significantly less and lost weight and all either died, aborted, or were killed in extremis. There were no significant maternal or fetal effects in the other groups (maternal NOEL = fetal NOEL = 12 mg/kg/day). No adverse effect was indicated. The study was unacceptable because there were no litters in the high dose group and no maternal effects in the intermediate or low doses (J. Kishiyama and S. Morris, 4/14/92) but upgraded to acceptable by submission of an adequate rationale for the intermediate dose being sufficient to test for developmental effects (S. Morris and J. Gee, 10/17/94).

> 311-046 121821: "Cacodylic Acid Preliminary Teratology Study in the Rabbit", LSRI Project No. PAL/018/CAC, 7/31/87. Six mated female HY/CR New Zealand White rabbits / group were dosed with 0, 5, 20, 40, or 80 mg/kg/day on post coitum days 7 through 19. The mortality rate of the treatment groups for the lowest to highest doses were respectively: 2/7, 1/6, 3/6, 1/6, and 6/6 ([found dead + killed in extremis + killed on humane grounds] / total animals). The high dose animals had decreased food consumption, weight gain, and passage of feces. There were no treatment-related effects on reproductive variables. The fetuses were not examined for abnormalities or deformations. Evaluation of these data did not result in a change in study status (see DPR Response 4/19/93). No worksheet was done (S. Morris, 4/19/93).

GENE MUTATION

**311-042 113766; "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", Laboratory Study Number T9785.501; R.H.C. San and M.L. Klug; Microbiological Associates, Inc., Rockville, MD; 5/24/91. Cacodylic acid (lot # 0030101, 99.95% stated purity) was tested in an assay that measured the mutation rate of *Salmonella typhimurium* bacteria (tester strains TA98, TA100, TA1535, TA1537, TA1538) from histidine auxotrophy to prototrophy in the presence or absence of a metabolic activation system derived from the S-9 supernatant of Aroclor 1254 induced, male, Sprague-Dawley rat liver homogenates (S-9). Using the plate incorporation technique, each strain was tested with or without S-9 in triplicate at 0 (water vehicle), 100, 333, 1000, 3333, or 10000 µg per plate. There was no treatment-related increase in mutation rate. No adverse effect was indicated. The study was unacceptable (S. Morris and J. Gee, 7/21/92) but upgraded by submission of adequate analysis of dosing solutions (S. Morris and J. Gee, 5/10/95) .

> 311-046 121820: This document contained data supplemental to DPR doc. # 311-042, rec. # 113766. This document contained adequated analysis of dosing solutions. The study was upgraded to acceptable. A worksheet was done (S. Morris, 5/10/95).

311-016 041618, "Evaluation of Herbicides for Possible Mutagenic Properties"; K.J. Andersen, E.G. Leighty and M.T. Takahashi; J. Agr. Food Chem. Vol. 20, No. 3, 1972; pp. 649-656. Technical cacodylic acid of unstated purity was tested in bacterial mutation assay using 8 strains of *Salmonella typhimurium* histidine-requiring mutants without metabolic activation. There were few experimental details and no data. The test material was negative. The study was unacceptable and not upgradeable. No worksheet was done (S. Morris, 4/6/92).

311-005 913606: This document contains an exact duplicate of 311-016 041618. A brief worksheet was done (J. Christopher, 3/4/85).

311-005 913605: This document contains a limited amount of summary data from mutagenicity assays using 5 strains of histidine auxotrophs of *Salmonella tryphimurium*, Fisher rat embryo cells infected with Rausher leukemia virus, and BALB/3T3 mouse cells. There were no data indicating the test material was mutagenic. A brief worksheet was done (J. Christopher, 3/4/85).

311-015 041617 This document contains no data. No worksheet was done (S. Morris, 4/3/92).

CHROMOSOME EFFECTS

**311-042 113767; "Micronucleus Cytotoxicity Assay in Mice", Laboratory Study Number T9785.122; D.L. Putman and M.J. Morris; Microbiological Associates, Inc., Bethesda, MD; 5/24/91. Cacodylic acid (lot # 0030101, 99.95% stated purity) was administered by single ip injection in 10 ml/kg water to 15 ICR mice/sex/dose at 0, 147, 293, or 586 mg/kg. Twenty-four, 48, or 72 hours later femural bone marrows samples were taken from 5 animals per sex. The samples were fixed and stained and 1000 polychromatic erythrocytes per animal were microscopically scored for micronuclei. Adequacy of dosing was demonstrated by mortality at doses $\geq$ 563 mg/kg in a preliminary test. The positive control using 30 mg/kg cyclophosphamide were adequate. There was no treatment-related increases in micronuclei. No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 8/8/92).

DNA DAMAGE

****311-042 113768**; "L5178Y TK +/- Mouse Lymphoma Mutagenesis Assay", Laboratory Study Number T9785.701; C.A. Bigger and J.J. Clarke; Microbiological Associates, Inc., Rockville, MD; 5/24/91. Cacodylic Acid (lot # 0030101, 99.95% stated purity) was tested in an assay that measured the rate of mutation of cultured mouse lymphoma cells from trifluorothymidine sensitive to resistant. Single aliquots of 6X106 cells were exposed for 4 hours to 0 (solvent control 1), 0 (solvent control 2), 1.6, 2.3, 2.7, 3.0, 3.6, 3.9, 4.8, 5.4, 5.8, or 7.7 without S-9 activation or at 0 (solvent control 1), 0 (solvent control 2), 1.6, 2.3, 2.7, 3.0, 3.2, 3.6, 4.0, 4.5, 4.8, or 5.8 mg/ml with S-9 activation. After removal of the test material, the cells were incubated for 48 hours in growth medium. Finally, triplicate aliquots of 3X105 cells were plated in the presence of 3 mg/ml trifluorothymidine and colony formation was assessed after 10 - 12 days incubation. A **possible adverse effect** was indicated by increased mutation rates at all doses of the test material with or without S-9. The study was acceptable (S. Morris and J. Gee. 7/24/92).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL

311-002 913576: This document contains brief summaries of 90-day feeding studies in rat and dog. The dietary levels for dog were 3, 15, or 30 ppm and for rat were 3, 15, or 100 ppm. The NOEL's for rat and dog were respectively 100 and 30 ppm. No other details or data are given. No worksheet was done (S. Morris, 8/11/92).

311-008 030960: This document contains a review article that cited 90-day feeding studies in rats and dogs. The NOEL's for rat and dog were respectively 100 and 30 ppm. No other details or data are given. No worksheet was done (S. Morris, 8/11/92).

311-012 913620: This document contains a review article that has one paragraph summaries of acute and subacute studies in a variety of species, a bacterial mutation study, oncogenicity study in mouse, and teratology studies in progress using rat and mouse. Insufficient details and data were given for evaluation. Brief worksheets were done (D. Shimer, no date).

311-013 020466: This document contains a partial duplicate of doc. # 311-012, rec. # 913620. No worksheet was done (S. Morris, 8/12/92).

289-023 041675; "*In Vivo* and *In Vitro* Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens", V.F. Simmon, A.D. Mitchell and T.A. Jorgenson; SRI, Menlo Park, CA; 2/77. This document contains summary data from the following assays: unscheduled DNA synthesis in human fibroblasts (Wi-38 cells); reverse mutation in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, and TA100 and in *Escherichia coli* WP2; mitotic recombination in the yeast *Saccharomyces cerevisiae* D3; and preferential toxicity assays in in DNA repair-proficient and -deficient strains of *E. Coli* (strains W3110 and p3478, respectively) and *Bacillus subtilis* (strains H17 and M45, respectively). The test material was negative in all tests. Insufficient details and data were given for evaluation. No worksheet was done (S. Morris, 8/11/92).

289-023 041676,
311-015 041615,
311-015 041616,
311-015 041617: These documents contain copies of 289-023 041675. No worksheets were done (S. Morris, 4/3/92).

50803-001 059705 - 059714: These documents contain protocols for a variety of test types. No worksheets were done (S. Morris, 8/12/92).

These documents have been reviewed.

311-008 030960
311-013 020466
311-015 041615
311-015 041616
311-015 041617
311-016 041618
289-023 041675
289-023 041676
50803-001 059705
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